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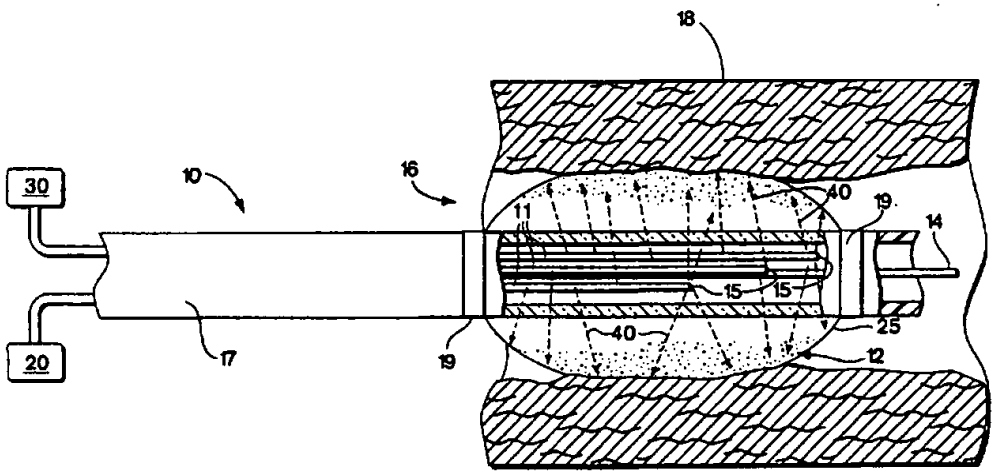

(57) Abstract

Photolytic release of a therapeutic or diagnostic agent from the surface of a drug-delivery device can be employed to accomplish site-specific drug delivery to body region, such as a lumen wall. In particular, the therapeutic agent can be photoreleasably bound to a polymer substrate contained on the exterior of the drug delivery device via a photoactivatable linking agent, such as a chromophore. Upon exposure to radiation, preferably UV radiation having a wavelength in the range of about 240 to about 370 manometers, the photoactivatable linking agent releases the therapeutic agent from the surface of the device onto the surrounding lumen wall. This drug delivery system provides a means for controlled site-specific, local delivery of drugs, chromophores, and nucleic acids to walls of various body lumens, such as blood vessels, with little or no damage to the surrounding tissue.

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PHOTOLYTIC DRUG DELIVERY SYSTEMS

Background of the Invention

This invention relates to methods and devices for photolytically delivering therapeutic agents to various vascular and non-vascular sites within the body.

Vascular injury associated with angioplasty procedures can initiate a complex cascade of biologic events, such as thrombosis, vascular smooth muscle cell migration and proliferation and production of extracellular matrix (see e.g., Ip, et al., *J. Am. Coll. Cardiol.* (1990) 7 : 1667-87; Cassells, W., *Circulation* (1992) 86 : 723-9; Schwartz et al., *J. Am. Coll. Cardiol.* (1992) 20 : 1284-93). Data from experimental and clinical studies have suggested that smooth muscle cell proliferation, in particular, represents a key event that ultimately leads to restenosis in up to 50% of all patients within the first 6 months after the intervention (see, e.g., Hanke et al., *Circ. Res.* (1990) 67 : 651-9; Pickering et al. *J. Clin. Invest.* (1993) 91 : 1469-80). When restenosis occurs, further coronary difficulties can be experienced, including strokes, arrhythmia, infarcts and even death.

The systemic administration of antithrombotic and antiproliferative agents in clinical studies, however, has thus far failed to achieve a significant reduction in the incidence of restenosis (Schwartz et al., *supra*). One explanation for the failure of such trials is that submaximal doses of standard pharmacologic agents have been used because of concerns that serious side effects might result from systemic administration of the required doses. The concept of local, intravascular, site-specific delivery of pharmacologic and biologic therapies has evolved as a solution (see, e.g., March et al., *Cardio Intervention* (1992) 2 : 11-26). This concept presumes that higher concentrations of a therapeutic agent may be achieved directly at the angioplasty site, thus avoiding the toxicity associated with systemic levels of the therapeutic agent.

The inhibition of smooth muscle cell proliferation has been the primary target for local intravascular drug delivery so far. However, the local delivery approach is likely to prove useful for treating a variety of other cardiovascular diseases as well. This includes local delivery of antithrombotic agents, antibiotics, genes, vectors and other biological agents to vascular segments prone to thrombosis, local deposition of angiogenic growth factors designed to promote neovascularization of an ischemic focus and local administration of agents designed to selectively alter vasomotor tone.

Approaches for local, intravascular, site-specific delivery of therapeutic agents have included direct deposition of such agents into the vessel wall through an intravascular delivery system. These intravascular delivery systems generally employ balloon catheters

which are easily guided through blood vessels to a region in need of treatment and can then be inflated to fully contact and dilate the entire surrounding vessel wall. A therapeutic agent can then be delivered to the surrounding vessel wall, for example, by diffusion through the balloon or by hydrostatic pressure, as occurs when using a porous balloon catheter. However, clinical use of such catheters is limited by certain practical problems, such as leakage of the solution through side branches and relatively long incubation times of 15 to 30 minutes. Furthermore, the inflation pressure required to accomplish a satisfactory seal between the balloon and the surrounding vessel wall can lead to additional vessel injury proximal and distal to the target site, potentially increasing the proliferative response or creating a nidus for thrombus formation.

Other balloon catheters which have been used for drug delivery to blood vessel walls are drug-coated catheters (e.g., hydrogel catheters). Upon inflation of the balloon in a blood vessel, the therapeutic agent is "pressed" onto or into the surrounding vessel wall. However, the main disadvantage of this system is that drugs are rapidly washed off the balloon by exposure to the blood-stream during the catheter's passage to the site (see, e.g., Sheriff et al., *J. Am. Coll. Cardiol.* (1993) 21 : 188A). Typically, the balloon must be chaperoned by a protective sheath as the catheter is advanced toward the target vessel. Similarly, the time between sheath removal and balloon inflation must be minimized to avoid premature shedding of the drug into the blood stream at the site prior to balloon inflation.

As an alternative to drug delivery catheters, polymeric stents have also been used for sustained local drug delivery of antithrombotic or antiproliferative drugs, genes or the like. Several approaches have been investigated to achieve continuous drug release from a stent including, for example, seeding the stent with genetically modified endothelial cells to elute agents such as tissue plasminogen activator, and coating the stent directly with drugs or with drug-eluting biodegradable polymers.

There exists a need for improved methods and devices for local, intravascular delivery of therapeutic agents. A system which delivers a controlled amount of a therapeutic or diagnostic agent to a blood vessel wall, without creating additional tissue damage or significant inflammatory responses, would satisfy a great need in the art.

Summary of the Invention

Methods and devices are disclosed for photolytic local delivery of one or more therapeutic or diagnostic agents to a body region, such as a blood vessel wall. More specifically, the invention pertains to an intravascular or intraluminal drug delivery device having a therapeutic or diagnostic agent photoreleasably linked to its exterior surface. The linkage is mediated by a photoactivable agent, such as a chromophore,

which releases the therapeutic or diagnostic reagent from the exterior surface upon exposure to light. The term "therapeutic agent", as used herein, refers to any agent or combination of agents that may affect the cells or structure of a body region, including drugs, peptides, chromophores, nucleic acids, vectors, or the like, which can be used to treat, study or diagnose certain conditions within the body region.

Photoactivatable agents suitable for releasing the bound therapeutic or diagnostic agent from the surface of a medical device include any agent which can be linked to a functional group (e.g., a phenol) of the therapeutic or diagnostic agent and which, upon exposure to light, releases the therapeutic or diagnostic agent in functional form. In one embodiment, the photoactivatable agent is a chromophore. Suitable chromophores are generally selected for absorption of light that is deliverable from common radiation sources (e.g. UV light ranging from 240-370 nm). Examples of chromophores which are photoresponsive to such wavelengths include, but are not limited to, acridines, nitroaromatics and arylsulfonamides.

When using chromophores, the efficiency and wavelength at which the chromophore becomes photoactivated and thus releases or "uncages" the therapeutic agent will vary depending on the particular functional group(s) attached to the chromophore. For example, when using nitroaromatics, such as derivatives of o-nitrobenzylic compounds, the absorption wavelength can be significantly lengthened by addition of methoxy groups. In one embodiment, nitrobenzyl (NB) and nitrophenylethyl (NPE) is modified by addition of two methoxy residues into 4,5-dimethoxy-2-nitrobenzyl (DMNB) and 1-(4,5-dimethoxy-2-nitrophenyl)ethyl (DMNPE), respectively, thereby increasing the absorption wavelength range to 340-360 nm (λ_{max}= 355 nm).

To deliver the therapeutic agent to a specific body region, the drug delivery device of the invention can be guided into a position adjacent to the region to be treated, using conventional techniques. After positioning the device adjacent to the region to be treated, the device can be inflated or expanded so that its drug-containing exterior comes into contact with the surrounding tissue. Light is then transmitted to the drug derivitized surface of the device, e.g., by transmission throughout the interior of the device, causing photolytic release of the therapeutic agent from the exterior of the device onto the surrounding tissue.

Suitable medical devices for use in the invention include, for example, balloon catheters, endoscopes, polymer stents, and the like. In one embodiment of the invention, a conventional balloon angioplasty catheter containing one or more optical fibers is

modified by photoreleasably linking a therapeutic agent to the exterior of the balloon. The catheter is guided into position adjacent to an area to be treated using, for example, a guide wire, and the balloon is then inflated so as to contact and dilate the surrounding tissue. Following inflation of the balloon, radiation from an irradiation source is delivered via one or more optical fibers which extend through the terminal end of the catheter into the balloon. A diffusive radio-opaque tip is optionally attached to the terminal end through which the radiation is delivered and scattered throughout the balloon. The light delivered through the balloon subsequently causes photolytic release of one or more therapeutic agents bound to the exterior of the balloon, thereby delivering the therapeutic agent to the surrounding body tissue. If the therapeutic agent itself is photoactivatable (e.g., a photoactivatable psoralen or hematoporphyrin), then the light delivered through the balloon can also be used to activate the therapeutic agent, following its delivery to the surrounding body tissue.

Radiation to promote photorelease of the therapeutic or diagnostic agent can be provided by a variety of sources including, but not limited to, non-coherent UV light sources and excimer sources. In one embodiment, a KrF excimer laser operating at 248 nanometers can be used. Alternatively, a frequency-quadrupled, solid state, Neodymium-doped YAG laser or the like operating at 266 nm can be used, or an Argon ion laser operating at 257 or 275 nm can be used.

In order to photoreleasably link a drug or therapeutic agent to the exterior surface of a drug delivery device, or a portion thereof, the surface is generally first primed with a substrate, typically an organic polymer, having functional groups available for reaction with a photoactivatable linking agent. In one embodiment, the substrate is an acrylic derivative such as, polymethacrylic acid. Other polymers which can be used include, but are not limited to, polyacrylamides, polyethylene, polystyrene, polyethylene terephthalate (PET), polypropylene, polyolefin, polyurethane and other thermoplastic elastic polymers. Polymer resins, such as methylbenzhydrylamine, and copolymers, for example copolystyrene-divinylbenzene, can also be used. Non-polymer surface chemistries may also be employed. For example, metallic, glass or silica-based surfaces can be modified with, for example, dialkyldichlorosilanes to provide a reactive surface suitable for further derivatization.

The photoactivatable agent can then be linked to the substrate either alone or following its attachment to the drug or compound to be delivered. Linkage to the substrate can be achieved using, for example, solution-phase conjugation (i.e., contacting the interface of the substrate with a liquid carrying the photoactivatable agent or the photoactivatable agent-drug conjugate). Alternatively, linkage can be achieved by direct

reaction of the photoactivatable agent or the photoactivatable agent-drug conjugate on the substrate.

Either prior to or following its attachment to the substrate, the photoactivatable agent is reacted with the therapeutic agent to create a photoreleasable linkage. When using chromophores as photoactivatable agents, the excitation wavelength may be chosen so as to selectively excite particular chromophores. For example, it is possible to photoreleasably attach two different drugs or to two different chromophores to the substrate, and then independently or sequentially release the two drugs by selecting the excitation wavelength to match the corresponding chromophore. The chromophore and the excitation wavelength may further be selected to avoid undesired photolytic reactions of the drug (e.g., inactivation) or of the surrounding tissue. For example, the photosensitivity of nucleic acids is well known. When the drug is a nucleic acid, excitation energy which may damage the nucleic acid (e.g. wavelengths shorter than 280 nm) should be avoided.

Use of photoactivatable linking reagents for controlled release of a therapeutic agent from the surface of a drug delivery device is a safe and effective means for locally delivering drugs and other biologicals to any body tissue, particularly blood vessel walls. As noted above, therapeutic agents which can be delivered by this method include any agent or combination of agents that may affect the cells in the vessel wall, including drugs, chromophores, and nucleic acids. Therapeutic agents also include diagnostics which will aid in later treatment, such as radiopaque compounds that allow the vessel to be visualized by fluoroscopy or similar methods. Therapeutic agents may further include antimicrobial agents, such as antibacterial and antiviral agents.

For restenosis inhibition, it is typically desirable to arrest the proliferation of smooth muscle cells. Accordingly, drugs which prevent platelet aggregation and adhesion can be used, such as antiplatelets and anticoagulants. In addition, receptor blockers, growth factors and other hormones may be used to limit the normal repair response. The following are groups of particular drugs which can be used to treat vascular disease, such as atherosclerosis and restenosis: anticoagulants, including heparin, hirudin, hirulog, tissue plasminogen activator, and fibrinogen; anti-inflammatory agents, such as steroids, ibuprofen, aspirin, somatostatin, angiopeptin, and anti-inflammatory peptide 2; cytotoxins, including colchicine, dexamethasone, doxorubicin, methotrexate, and psoralen; antibiotics; and enzymes and enzyme inhibitors, including urokinase, 2,4-dinitrophenol, and thiol protease inhibitor.

Alternatively, photoactivatable chemical agents which inhibit smooth muscle cell proliferation upon exposure to light can be used as therapeutic agents to prevent restenosis. For example, photoactivatable psoralens and hematoporphyrins can significantly inhibit the proliferation of smooth muscle cells within blood vessel walls upon irradiation with long-wave UV light (PUVA) (see e.g., U.S. Patent No. 5, 116, 864 (March et al.). Accordingly, these photoactivatable agents can be photolytically delivered to specific tissue, such as a region of a blood vessel wall, by the devices and methods of the present invention. In one embodiment, the photoactivatable agent is releasably linked to the substrate (contained on the exterior of the drug delivery device) in an inactive form, and then photolytically delivered to an adjacent area of tissue, as previously described. Once delivered to the targeted tissue, the agent is activated by exposure to radiation of an appropriate wavelength.

The drug delivery devices and methods of the present invention can also be used for local, site-specific gene and antisense therapies. In particular, genes, or vectors containing genes, can be delivered which express proteins involved in modulating biologic processes in a body region, such as cell proliferation or matrix production by autocrine means. For example, genes which overexpress non-secreted growth inhibitors (e.g., tumor suppressor genes) can be transfected into smooth muscle cells present in blood vessel walls to prevent restenosis or proliferation of the cells. Alternatively, to prevent restenosis, genes encoding proteins which cause the death of smooth muscle cells upon exposure to certain drugs can be delivered to blood vessel walls. In one embodiment, genes encoding thymidine kinase are transfected into vascular smooth muscle cells, rendering the cells vulnerable to gancyclovir.

The devices and methods of the present invention can also be used to treat blood vessel and arterial blockages. In one embodiment, genes encoding growth factors, such as vascular endothelial growth factor (VEGF), which stimulate new blood vessel growth, are delivered to the walls of blocked vessels to promote the generation of new vessels which bypass the obstruction.

Overall, the methods and drug delivery devices of the present invention provide a safe and effective means for local, site-specific delivery of a wide variety of therapeutic agents to vascular and other body tissues. Unlike conventional drug-coated catheter devices which rely on significant pressure to release therapeutic agents from the catheter surface to the surrounding vessel wall, the systems provided by the present invention use non-damaging radiation to photolytically release the therapeutic agent.

The drug delivery systems provided by the invention also help avoid the problem of overdosage associated with systemic delivery of drugs, by enabling a controlled amount of a selected therapeutic or diagnostic agent to be directly deposited onto a specific region of tissue. Furthermore, the systems allow for selective delivery of therapeutic or diagnostic agents to vessel walls by using photoactivatable linking agents having differing absorption profiles. The system also solves the problem of drug wash-off or leakage by photoreleasably linking the drug to the exterior of the delivery device. The system further solves the problem of adverse immunogenicity associated with implantable stents, since the catheter is removed immediately following drug delivery.

Brief Description of the Drawings

FIG. 1 is an illustration of a photolytic drug delivery device for insertion into a body lumen.

FIG. 2 is a schematic illustration of the photolytic release of a bioactive ligand from a polymer-coated surface matrix using a chromophoric linker to sensitize the cleavage reaction.

Detailed Description

In **FIG. 1**, a drug delivery device **10** for photolytic delivery of one or more therapeutic or diagnostic agents to a body lumen wall is shown, including inflatable section **25** and a guide wire **14**. Also disposed within the device are one or more optical fibers **11** for delivery of radiation **40** which causes photolytic release of the drug or therapeutic agent **12** from the the exterior of the device **25**. The optical fibers **11** can be disposed around the central guide wire **14**, as shown in **FIG. 1**. The drug delivery device can also optionally include a diffusive tip **15** and a radio-opaque tip marker **19**.

To use the drug delivery system **10**, the guide wire **14** is first introduced into a body lumen and used to guide the device into position adjacent to an area to be treated, such as a stenotic lesion. As shown in **FIG. 1**, the inflatable section **25** is then expanded which applies pressure against the surrounding lumen wall **18**. If the area being treated is obstructed, expansion of the inflatable section **25** serves to dilate the obstruction. Expansion and contraction of the inflatable section **25** is controlled by an inflation controller **20**. In all cases, the inflatable section **25** is expanded so as to be in full contact with the surrounding lumen wall **18**.

Following expansion of the inflatable section **25**, radiation from an irradiation source **30** is delivered via one or more optical fibers **11** which extend through the terminal end of the device **16** into the inflatable section **25**. In one embodiment, a diffusive radio-opaque tip is

attached to the terminal end through which the radiation is delivered and scattered throughout the inflatable section **25**. The light delivered through the inflatable section **25** subsequently causes photolytic release of a therapeutic or diagnostic agent **12** bound to the exterior surface of the inflatable section **25**, thereby delivering the therapeutic or diagnostic agent to the surrounding lumen wall **18**.

Any medical device may be used in the photolytic drug delivery system of the invention, following modification to include a source of radiation and one or more therapeutic agents photoreleasably linked to its exterior surface. Typically, a fiber optic track is incorporated through the body of the device **17** so that light can be delivered throughout the interior of the device. The optical fibers **11** may be of any type appropriate to deliver radiation required for photolytic release of the drug from at least a portion of the exterior of the device.

The optical fibers **11** are connected to a radiation source **30**. The source can be a UV light source which delivers light having a wavelength ranging from about 200 to about 400 nanometers, more preferably from about 240 to about 370 nanometers. The radiation can be provided by a variety of sources, including non-coherent UV light sources and excimer laser sources (e.g., a KrF excimer laser operating at 248 nanometers or an Argon ion laser at 257 or 275 nm.)

In **FIG. 2**, a reaction scheme for photolytically releasing a bioactive ligand from a polymer-coated surface matrix using a chromophoric linker to sensitize the cleavage reaction is shown. Attachment of the chromophoric linker and bioactive ligand to the surface matrix of a medical device may be accomplished by way of several methods known in the art (for examples of surface chemistries, coupling reagents, and protecting groups, see e.g. M. Bodanszky, Principles of Peptide Synthesis, 2nd Ed. (1993) and references cited therein). In some cases, an additional chemical linking or spacing arm may be preferable to achieve the desired chemical stability or loading. Furthermore, the surface matrix of the device may benefit from chemical modification before the chromophoric linker can be attached (for examples of linkers, surface chemistries, and several chromophores, see Grant, G.R., Ed. *Synthetic Peptides: A User's Guide* (1992), Chapter 3). Methods for derivatization of surfaces are well known in the art. A variety of functional groups, for example aminoalkyl, benzhydrylamino, halobenzyl, haloalkyl, phenol, alkoxy or carboxylate groups, can be formed on the surface installed by choice of an appropriate derivative.

This invention is illustrated further by the following examples which should not be construed as further limiting the subject invention. The contents of all references and

published patent applications cited throughout this application are hereby incorporated by reference.

Example 1

Photolytic Delivery of Somatostatin

Somatostatin, a growth hormone inhibitor, can be used to effectively inhibit smooth muscle cell growth. To prepare a device for photolytic delivery of somatostatin to a specific region of a body lumen (e.g., a stenotic lesion), the following procedure can be used. In this procedure, a photoactivatable agent, 3-nitro-4-(N-dithiasuccinimido)methyl benzoic acid, is linked to the surface of a device containing a light source. The drug moiety is then releasably coupled to the photoactivatable moiety.

To link the photoactivatable moiety to the surface of the device, the exterior of the device is first coated with an amino-functionalized polystyrene substrate, using standard techniques. The polystyrene substrate is then derivatized with the 3-nitro-4-(N-dithiasuccinimido)methyl benzoic acid, a protected photoactivatable linking moiety, under standard coupling conditions (see F. Albericio et al., Peptides: Chemistry and Biology: *Proceedings of the Tenth American Peptide Symposium*, G.R. Marshall, Ed. ESCOM: Leiden (1988), p. 159-161).

Somatostatin is then releasably linked to the dithiasuccinimido-protected photoactivatable moiety by removing the dithiasuccinimido group, for example, by reaction with 2-mercaptoethanol and triethylamine for 5 minutes, to yield the free amine. The unprotected benzylamine functionality is then coupled to the carboxy terminal of somatostatin, using the coupling reagent dicyclohexyl-carbodiimide (DCC).

To photolytically deliver somatostatin to a specific region of a lumen wall, the device is guided through the lumen into a position adjacent to the region. The device is then expanded so as to cause its drug-containing surface to come into contact with the surrounding lumen wall. Following expansion of the device, its interior is irradiated via one or more optical fibers which emit light having a wavelength of approximately 350 nm, thereby activating the benzylamine chromophore on the exterior of the device. Photoactivation of the benzylamine then causes release of the somatostatin (as the C-terminal amide) onto the surrounding lumen wall.

Example 2

Photolytic Delivery of Ibuprofen

Ibuprofen, an analgesic agent, has useful antiinflammatory properties and can be used to treat inflammation within a body lumen. To prepare a drug-delivery device for photolytic delivery of ibuprofen to a specific region of a body lumen, the following procedure can be used. In this procedure, a photoactivatable linking agent, 2-nitroaniline, is linked to the surface of a device containing a source of light. Ibuprofen is then releasably linked to the photoactivatable agent.

First, the device is coated with a polystyrene substrate. The polystyrene substrate is then derivatized according to standard protocols (see e.g. Merrifield, R.B. *J. Am. Chem. Soc.* (1962) 85 : 2149), to yield the reactive chlorobenzyl derivative. Following its modification, the substrate is reacted with the photoactivatable linking agent, 2-nitroaniline (Amit, B. and Patchornik, A. *Tetrahedron Lett.* (1973) 24 : 2205), yielding an immobilized chromophore. Ibuprofen is then coupled to the chromophore-containing device under standard conditions using the coupling reagent DCC.

To photolytically deliver the ibuprofen to a specific region of a lumen wall, the device is guided through the lumen into a position adjacent to the region. The device is then expanded so as to cause its drug-containing surface to come into contact with the surrounding lumen wall. Following expansion of the device, its interior is irradiated via one or more optical fibers which emit light having a wavelength of approximately 350 nm, thereby activating the immobilized 2-nitroaniline chromophore on the exterior of the device. Photoactivation of the 2-nitroaniline then causes release of the ibuprofen onto the surrounding lumen wall.

Example 3

Photolytic Delivery of Lovastatin

Lovastatin, an inhibitor of HMG-CoA reductase, has found clinical use as a cholesterol-lowering agent. Consequently, site-specific delivery of lovastatin to body lumen walls which contain, or potentially could contain, fatty cholesterol build-up could be useful. A drug-delivery device which achieves this goal by photolytically delivering lovastatin to a specific region of a body lumen wall can be prepared according to the following procedure. In this procedure, the drug and a photoactivatable linking agent, 2-(p-chlorosulfonyl)phenyl t-butyl acetate, are first coupled together. The drug-linker conjugate is then coupled to the surface of a device containing a light source to yield a complete drug delivery system.

To link the photoactivatable linking moiety to lovastatin, 2-(p-chlorosulfonyl)phenyl t-butyl acetate (synthesized from commercially available starting materials) is reacted with the drug under standard conditions to produce a sulfonate-linked drug-chromophore conjugate. The t-butyl ester is then converted to the free carboxylic acid by brief exposure to acidic conditions.

Following conjugation of the photoactivatable linking agent with lovastatin, the conjugate is linked to the surface of a device containing a light source, as follows: The device is coated with a poly(acrylic acid) substrate using standard techniques. The polymer is then reacted with ethylenediamine (which functions as a linking or spacing arm) in the presence of a coupling reagent such as DCC or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) to yield an amine-functionalized polymer substrate. The drug-chromophore conjugate is then coupled, via the carboxylate, to the amine-functionalized polymer with the coupling reagent DCC, to yield the photoreleasably-immobilized drug.

To photolytically deliver the lovastatin to a specific region of a lumen wall, the device is guided through the lumen into a position adjacent to the region. The device is then expanded so as to cause its drug-containing surface to come into contact with the surrounding lumen wall. Following expansion of the device, its interior is irradiated via one or more optical fibers which emit light having a wavelength of approximately 300 nm, thereby activating the sulfonate chromophore on the exterior of the device. Photoactivation of the arylsulfonate then causes release of the lovastatin onto the surrounding lumen wall.

Equivalents

Those skilled in the art will be able to recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific compositions and procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

What we claim is:

1. A method of delivering a therapeutic agent to a body region, the method comprising:

disposing a medical device inside a body region, the device having at least one therapeutic agent photoreleasably bound to its exterior surface;

locating the device adjacent to a region of tissue to be treated;

irradiating the device surface so that the therapeutic agent is released on to the adjacent tissue.

2. The method of claim 1, wherein the method further comprises applying a substrate to said device surface to facilitate attachment of said photoreleasable agent.

3. The method of claim 1, wherein the method further comprises employing a linking compound to join the agent to the surface.

4. The method of claim 1, wherein the irradiating step further comprises irradiating the interior of the device with light having sufficient energy to propagate through the device and release the agent on the exterior surface.

5. The method of claim 1, wherein the irradiating step further comprises irradiating the interior of the device with light at a plurality of wavelengths sufficient to release onto the surrounding lumen wall a plurality of agents responsive to different wavelengths.

6. The method of claim 1, further comprising the step of irradiating the therapeutic agent released onto the adjacent tissue with radiation sufficient to activate the therapeutic agent.

7. The method of claim 1, wherein the step of irradiating the interior surface of the device comprises irradiating with UV light.

8. The method of claim 7, wherein the UV light has a wavelength of about 240 to 370 nanometers.

9. The method of claim 1 wherein the therapeutic agent is also activated by said radiation upon release.

10. A method of sequentially delivering at least two therapeutic agents to a target area of a body region, the method comprising:

disposing a medical device inside the body region, the device having at least two therapeutic agents photoreleasably bound to its exterior surface, said agents being bound to the surface via a photoactivatable linking agents having different activation wavelengths;

locating the device adjacent to the target area of the body region;

irradiating the interior of the device with light of at least two different wavelengths sufficient to activate each of the photoactivatable linking agents, so that the therapeutic agents are each released onto the body region.

11. A drug delivery device having a body with at least one surface adapted to contact body tissue, at least one therapeutic agent photoreleasably bound to the surface, and means for irradiating the agent and effecting its release onto the body tissue.

12. The device of claim 11 wherein the irradiation means is a UV light source.

13. The device of claim 11 wherein the irradiation means is a laser.

14. The device of claim 11 wherein the surface further comprises a substrate and a photoactivatable linker which links the therapeutic agent to the substrate.

15. The device of claim 14, wherein the substrate further comprises a polymer.

16. The device of claim 14, wherein the linker further comprises a chromophore.

17. The device of claim 16, wherein the chromophore further comprises a nitroaromatic.

18. The device of claim 16, wherein the chromophore further comprises an acridine.

19. The device of claim 16, wherein the chromophore further comprises an arylsulfonamide.

20. The device of claim 11, wherein the irradiation means further comprises an optical fiber for delivering radiation.

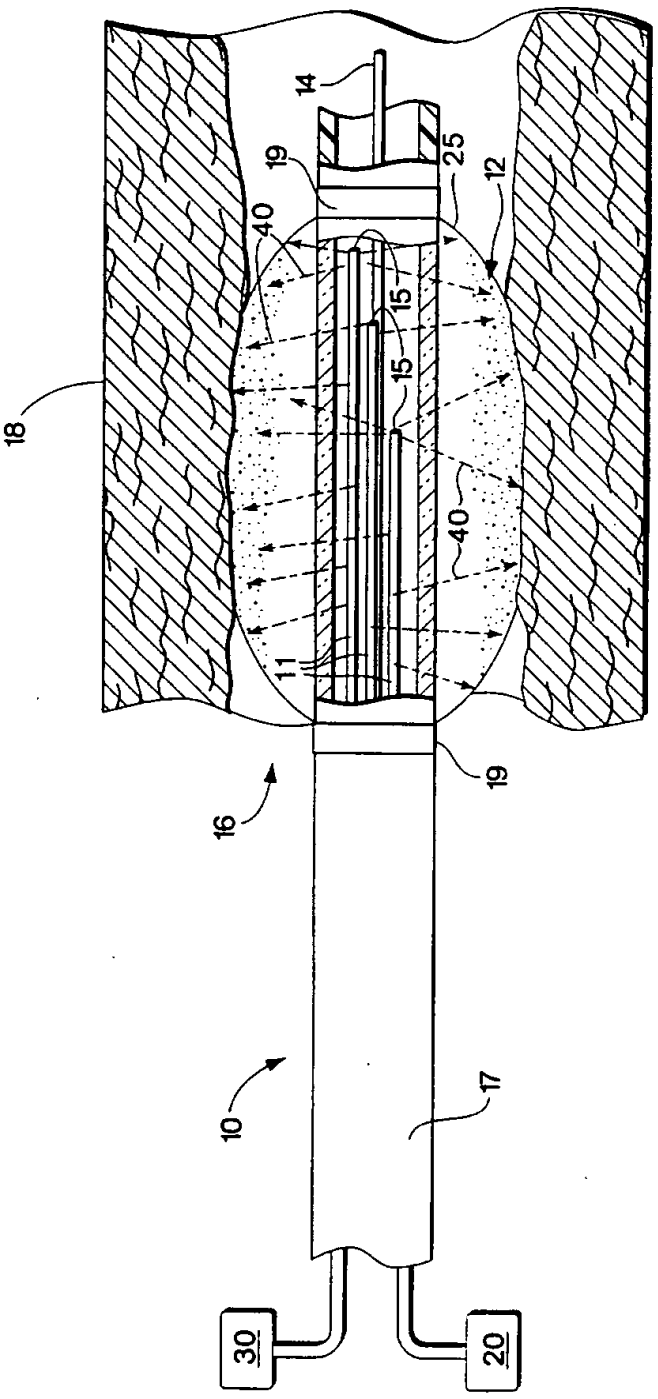

Fig. 1

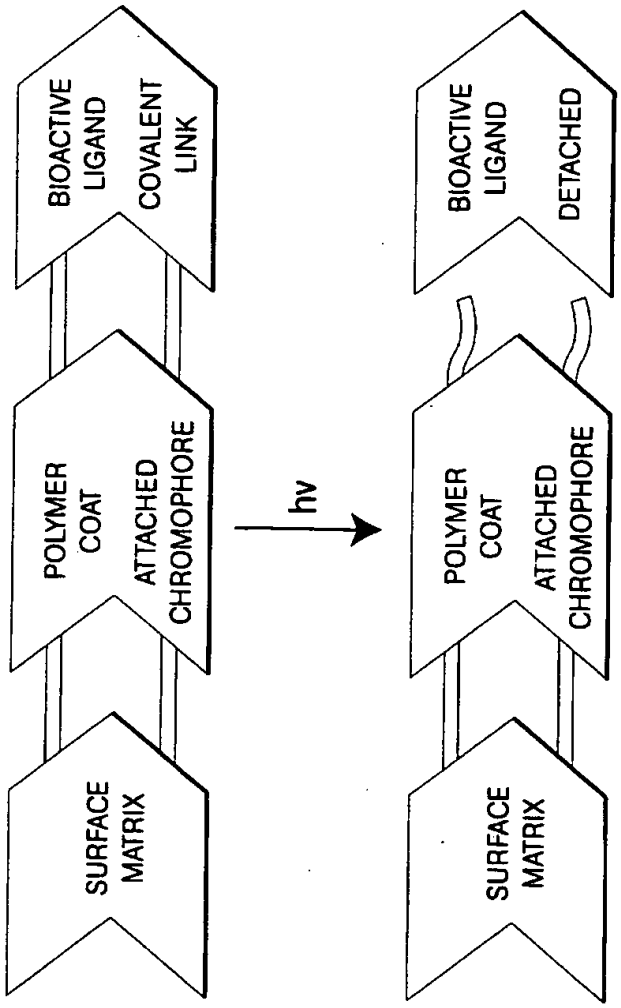
BIOACTIVE LIGAND
COVALENT LINK
POLYMER COAT
ATTACHED CHROMOPHORE
SURFACE MATRIX
hv
BIOACTIVE LIGAND
DETACHED
POLYMER COAT
ATTACHED CHROMOPHORE
SURFACE MATRIX

Fig. 2

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/01333

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M29/02 A61K41/00 A61B17/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A61K A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,5 102 402 (MEDTRONIC, INC.) 7 April 1992 see column 2, line 5-37 see column 4, line 14-61 see figures 1,3,7 ---	11-17,20
Y	WO,A,94 09826 (MEDIPRO SCIENCES LIMITED) 11 May 1994 see page 1, line 1-22 see page 2, line 8 - page 3, line 5 see page 4, paragraph 2 see page 4, paragraph 3 see page 5, paragraph 2 see page 9, paragraph 2 see page 11 see page 37, paragraph 2 --- -/--	11-17,20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
9 May 1996	04.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Bichlmayer, K-P

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/01333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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